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(54) Title: COMPOSITIONS AND METHODS FOR REDUCING OCULAR HYPERTENSION

(57) Abstract

An improved ophthalmic composition, including prostaglandin active agents, which is especially useful in lowering intraocular pressure associated with glaucoma. Improvements in IOP reduction efficacy, preservative efficacy and reduced additive concentrations are achieved by utilizing the disclosed compositions which include a prostaglandin active agent (e.g., isopropyl unoprostone, a metabolite of an F–series prostaglandin), in conjunction with selected non–ionic surfactants, preservatives, and non–ionic tonicity adjusting agents.

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COMPOSITIONS AND METHODS FOR REDUCING OCULAR HYPERTENSION

The invention relates broadly to ophthalmic technology. More specifically, this invention relates to therapeutic treatment of the eye or ocular tissue to reduce elevated intraocular pressure, for example, elevated intraocular pressure which is associated with glaucoma.

2. DESCRIPTION OF THE RELATED ART

The use of prostaglandins as medicaments is known in the art. For example, U.S. Patent Nos. 5,106,869 and 5,221,763 disclose the use of 13,14-dihydro-15-keto PGFs (F-series prostaglandins) for raising blood pressure without substantial ephemeral depression of blood pressure which occurs with many PGFs.

Also, the use of prostaglandin active agents to treat certain ocular conditions is known in the art. The term "prostaglandin active agent", as used herein, refers to prostaglandins, metabolites thereof, derivatives thereof, salts thereof, prodrugs of prostaglandins and mixtures thereof. For example, U.S. Patent Nos. 5,001,153; 5,151,444; 5,166,178 and 5,212,200 disclose the use of 13,14-dihydro-15-keto prostaglandin metabolites to reduce ocular pressure without causing a transient ocular hypotension response which prostaglandins usually cause. These patents discuss a collyrium (i.e., eyewash) which may include water as a diluent, BAK or NaCl as an isotonizing agent, borate or phosphate buffers, EDTA as a stabilizer, and a polysorbate surfactant.

Furthermore, U.S. Patent No. 5,208,256, issued to Ryuji Ueno on May 4, 1993 teaches a method of treating ocular hypotension by ocularly administering a combination of 13,14-dihydro-15-keto-20-loweralkylprostaglandin, or salt or ester thereof, and a polyoxyethylene-sorbitan unsaturated higher aliphatic acid monoester. Preferred examples of the latter includes miristoleic acid, palmitoleic acid, oleic acid, gadoleic acid and linoleic acid. Polyoxyethylene (20) sorbitan monooleate is also known as Polysorbate 80 and sold, *inter alia*, under the names SORLATE, CRILLET, TWEEN 80, MONITAN and OLOTHORB.

With regard to ophthalmic surfactants, CREMOPHOR has been used as a surfactant in eye drops (See Japanese Patent 07316060, filed on Dec. 16, 1994). CREMOPHOR is a ethoxylated, hydrogenated caster oil, which is also referred to as a polyoxyethylene hardened caster oil. However, the use of CREMOPHOR with prostaglandins in an ophthamic delivery system has not been disclosed or suggested.

While prostaglandin active agents, especially 13,14-dihydro-15-keto prostaglandin metabolites, are advantageous in reducing intraocular pressure, there is a need to improve the efficacy of these medicaments. In addition, there is a need for improvements in the preservative effectiveness of ophthalmic prostaglandin compositions which include surfactants, while maintaining good efficacy and good ocular tolerance. Furthermore, the improvements in shelf life of ophthalmic prostaglandin compositions are desirable. Also, it is always desirable to reduce the manufacturing difficulties. Moreover, there is a need for a prostaglandin-containing ophthalmic composition which can be manufactured with a minimum of complexities and which exhibits a balance of efficacy, preservative effectiveness, ocular tolerance, and a long shelf life.

SUMMARY OF THE INVENTION

An object of the invention is to improve the efficacy of prostaglandin-containing ophthalmic compositions.

Another object of the invention is to improve the preservative effectiveness of prostaglandin-containing ophthalmic compositions.

Still another object of the invention is to improve shelf life of prostaglandin-containing ophthalmic compositions.

Yet another object of the invention is to reduce the complexity of manufacturing a prostaglandin-containing ophthalmic composition.

A further object of the invention is to produce a prostaglandin-containing ophthalmic composition with a desirable balance of efficacy, preservative effectiveness, ocular tolerance, and shelf life.

These and other objects and advantages of the invention are achieved with the various embodiments of the present prostaglandin-containing ophthalmic compositions, methods of use and methods of manufacture. One embodiment of the invention is an ophthalmic composition which includes a prostaglandin, a non-ionic surfactant (e.g. a CREMOPHOR) and a preservative (e.g. benzalkonium chloride). Another embodiment is an ophthalmic composition which includes a prostaglandin, a surfactant, a non-ionic tonicity adjusting

agent (e.g. mannitol) and a preservative. Still another embodiment is an ophthalmic composition which includes a prostaglandin, a surfactant, a strong preservative (e.g. BAK) and a preservative enhancer (e.g., EDTA). Yet another embodiment of the invention relates to adding a buffer to improve product shelf life and reduce production complexities.

DESCRIPTION OF THE PREFERRED EMBODIMENTS

The various embodiments of the invention offer a number of improvements in prostaglandin compositions which are useful, *inter alia*, for reducing intraocular pressure. The compositions are especially useful in treating elevated intraocular pressure associated with glaucoma. Accordingly, all of the components of the compositions are preferably ophthalmically acceptable, at the concentrations of use and under the conditions in which they are applied. An "ophthalmically acceptable" component, as used herein, refers to a component which will not cause any appreciable ocular damage or ocular discomfort at the intended concentration and over the time of intended use.

I. EXEMPLARY EMBODIMENTS OF THE INVENTION

The invention embraces several embodiments, some of which are outlined below to improve the reader's understanding. One group of embodiments of the invention are ophthalmic compositions which are useful in reducing intraocular pressure, especially intraocular pressure which is associated with glaucoma. The ophthalmic compositions include an amount of a prostaglandin active agent selected from the group of prostaglandins, metabolites thereof, salts thereof, derivatives thereof or combinations thereof, which is effective in treating elevated intraocular pressures. Another group of embodiments are methods of reducing intraocular pressure and treating glaucoma by topical application of the aforementioned ophthalmic compositions. However, a person having ordinary skill in the art may vary some of the elements of the embodiments without departing from the spirit and scope of the invention.

One embodiment of the invention is a composition which has a reduced concentration of strong preservative, and correspondingly, generates less ocular irritation. Unexpectedly, it has been found that the use of certain non-ionic tonicity adjusting agents enhances the preservative effectiveness of strong preservatives in compositions containing prostaglandin active agents. This allows for a reduced concentration of strong preservatives in the composition. In addition, chelating agents may be added to further boost preservative efficacy and reduce the required concentration of strong preservative. Thus, one

embodiment of the invention is a composition which includes (1) a prostaglandin active agent (e.g. isopropyl unoprostone), (2) a strong preservative (e.g., benzalkonium chloride), and (3) a non-ionic tonicity enhancing agent (e.g., a simple sugar such as mannitol) effective in increasing the preservative efficacy relative to a composition including solely a strong preservative.

In particular, the complete erradication of *Pseudomonas Aeriginosa* is desired. While benzalkonium chloride (BAK) kills nearly all *Pseudomonas*, there may remain some which are resistant to BAK. Over time, the BAK-resistant *Pseudomonas* may propagate to a concentration which is unacceptable. Thus, it is preferably to include a preservative efficacy enhancer to eliminate BAK-resistant *Pseudomonas*.

It is preferable that the preservative efficacy enhancer or second preservative be a well tolerated component which acts via a mechanism which differs from BAK. The strong preservative (e.g., BAK) will handle the bulk of the bioburden. The use of the second well tolerated preservative or enhancer insures complete kill of contaminating microbes and yet minimizes ophthalmic irritation as compared to using abnormally high concentrations of BAK. This is accomplished by choosing a well tolerated additive whose mechanism of action differs from the strong preservative.

A preferred class of preservative efficacy enhancers are chelating agents, such as calcium chelating agents. A preferred calcium chelating agent is ethylene diamine tetraacetate (EDTA). EDTA has been shown to assist in the erradication of BAK-resistant *Pseudomonas* without substantially altering ophthalmic compatibility or prostaglandin efficacy. In addition, EDTA offers the advantage of simultaneously acting as a buffer.

Thus, in a preferred embodiment, the composition includes (1) a prostaglandin active agent, (2) a strong preservative, and (3) a non-ionic tonicity enhancing agent, (4) a chelating agent (e.g., edetate sodium). These compositions are especially advantageous in that preservative effectiveness is improved relative to a composition containing a strong preservative alone. This allows for a reduction in the required concentration of the strong preservative, and accordingly less ophthalmic irritation.

Another embodiment of the invention is a composition containing prostaglandin active agent which has an advantageously reduced total surfactant concentration. It is generally desirable to minimize the concentration additives to an ophthalmic formulation in order to

minimize potential ocular irritation associated with the additives. However, in order to solubilize prostaglandin active agents, a surfactant is typically required. It has been unexpectedly discovered that the combination of two or more non-ionic surfactants, as opposed to a single surfactant, can reduce the total concentration of surfactant required to achieve a given level of solubility of the prostaglandin active agent. Thus, this embodiment of the invention relates to a composition which includes (1) a prostaglanding active agent, (2) a first non-ionic surfactant (e.g., Polysorbate 80), (3) a second non-ionic surfactant [e.g., a BRIJ surfactant] and (4) an ophthalmically acceptable carrier. This embodiment of the invention offers advantages in reduced ocular irritation and reduced raw material (surfactant) requirements.

Yet another embodiment of the invention relates to the difficulties in achieving solubility of prostaglandin active agents. In order to solubilize the active agent, a non-ionic surfactant, preferably Polysorbate 80, is added to the formulation. Thus, increasing the prostaglandin concentration to the preferred ranges described herein requires a corresponding increase in the surfactant concentration, in order to maintain the prostaglandin in solution. However, the Polysorbate 80 surfactant deactivates the commonly used ophthalmic preservative benzalkonium chloride (BAK). Thus, an increase in surfactant reduces the preservative effectiveness. In sum, an increase in therapeutic efficacy which is achieved by increasing active agent concentration results in the need for an increase in Polysorbate 80 concentration and therefore a decrease in preservative effectiveness. Accordingly, improvements in both preservative effectiveness and efficacy of the cited formulations are difficult to achieve.

However, it has been unexpectedly found that the use of non-ionic tonicity adjusting agents appreciably improves the action of the preservative in the presence of surfactant. Thus, in order to minimize the aforementioned preservative deactivation problem, a preferred composition includes (1) a prostaglandin active agent, (2) a strong preservative (e.g., BAK), (3) a non-ionic surfactant which increases solubility of the prostaglandin active agent but decreases the preservative effectiveness of the strong preservative (e.g., Polysorbate 80), and (4) a preservative enhancer which increases the effectiveness of the strong preservative (e.g., mannitol or EDTA), and (5) an ophthalmically acceptable carrier. Thus, the efficacy and preservative effectiveness may be simultaneously improved in the present formulations, while maintaining a solution form, by optimizing the concentrations of active agent, surfactant, non-ionic tonicity adjusting agent, and preservative.

In contrast, some prior art prostaglandin formulations have used salts such as sodium chloride to adjust tonicity to ophthalmically acceptable levels (e.g., about 0.8 to about 1.0 mg/ml NaCl equivalents). However, ionic tonicity adjusting agents reduce the solubility of the prostaglandin-related active. Thus, another advantage of the use of non-ionic tonicity adjusting agents (e.g., mannitol) in the present invention is the increased solubility of salts of the active agent.

Still another embodiment of the invention is a buffered prostaglandin composition which offers improvements in manufacturing efficiency, improvements in shelf life and improvements in patient comfort. It is known that, for drops which are intended for direct instillation into the eye, a near neutral pH is preferred for patient comfort. In addition, adjustment of pH during manufacturing is difficult because of the small volume of solution in a consumer dispensing container. Further, the decomposition of the active prostaglandin over time increases formulation acidity, and increased acidity causes an increase in the rate of prostaglandin decomposition. Thus, the present embodiment is a prostaglandin composition which is buffered sufficiently to maintain a pH of about 4.5 to about 8.0 (preferably about 5 to 7.5, more preferably about 6 to 7.5) over a period extending from manufacturing to about a year of shelf life, preferably 2 years of shelf life. Preferred ophthalmically acceptable buffers include EDTA, borates, citrates, lactates and phosphates.

In accordance with several preferred inventive embodiment disclosed herein, a preferred composition includes:

(a) about 0.06 to about 0.24 weight percent isopropyl unoprostone;
(b) about 0.3 to about 2 weight percent of two non-ionic surfactant selected from the group consisting of CREMOPHOR RH, BRIJ 97, BRIJ 98, CREMOPHOR EL, Polysorbate 80 and mixtures thereof;
(c) about 0.01 to about 0.20 weight percent benzalkonium chloride;
(d) about 0.01 to about 0.1 weight percent EDTA;
(e) about 0.10 to about 10.0 weight percent mannitol;
(f) about 0.01 to about 0.05 molar of an ophthalmically acceptable buffer;
(g) an ophthalmically acceptable carrier;
in which the pH is adjusted to about 4.5 to about 8.0.

II. COMPONENTS OF THE COMPOSITIONS

A. ACTIVE AGENTS

The active agents useful in accordance with the invention may be selected from the group consisting of prostaglandins, metabolites thereof, derivatives thereof, salts thereof, prostaglandin prodrugs, and mixture thereof, referred to herein as "prostaglandin active agents" or merely "active agent". Thus, the active agent is not limited by the specific form of the active, i.e., whether in free acid or salt form. Rather, the prostaglandin active agent is active in that the agent causes a reduction of intraocular pressure (IOP) when applied to the ocular environment of a patient in need of reduction of intraocular pressure.

A prostaglandin, as used herein, refers to a group of fatty acids which include a prostanoic acid skeleton and which show various physiological activities. Prostaglandins are found in human and animal tissues and organs and may be synthetically produced. The preferred prostaglandins are those which are useful in therapeutic ophthalmic applications, especially those which reduce intraocular pressure.

A group of prostaglandins which have been found to be useful in decreasing intraocular pressure are disclosed in U.S. Patent Nos. 4,599,353; 5,296,504; 5,422,368; and 5,578,618. These patents are incorporated herein by reference for the teaching and examples of prostaglandin active agents which are useful in reducing intraocular pressure.

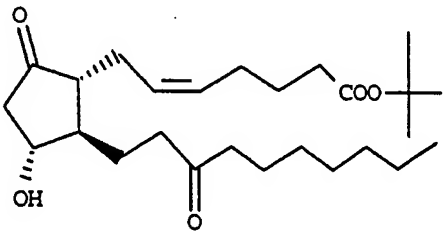
A particularly preferred group of active agents are certain prostaglandin metabolites. Preferred prostaglandin metabolites useful in ophthalmic applications are described more fully in U.S. Patent Nos. 5,106,869; 5,221,763 5,208,256; 5,001,153; 5,151,444; 5,166,178 and 5,212,200, each of which is incorporated herein by reference.

Prostaglandins of the present invention may be prostaglandin salts, or those prostaglandins with an esterified carboxyl group. Suitable prostaglandin salts are ophthalmically acceptable salts, including without limitation thereto, salts of alkali metals such as sodium or potassium; salts of an alkaline earth metal such as calcium or magnesium; salts of ammonia, methylamine, dimethylamine, cyclopentylamine, benzylamine, piperidine, monoethanolamine, diethanolamine, monomethylmonoethanolamine, tromethamine, lysine and tetralkylammonia; and the like and mixtures thereof. Suitable prostaglandin esters are ophthalmically acceptable esters, including without limitation thereto, methyl, ethyl, propyl, butyl, isopropyl, t-butyl, 2-ethylhexyl, straight or branched-chain alkyl esters which may contain an unsaturated bond. Suitable esters include an ester having an alicyclic group such as a cyclopropyl, cyclopentyl, olr cyclohexyl group; an ester containing an aromatic group such as a benzyl or phenyl group (wherein the aromatic gropu may contain one or

more substituents); a hydroxyalkyl or alkoxyalkyl ester such as hydroxyethyl, hydroxyisopropyl, polyhydroxyisopropyl, methoxyethyl, ethaoxyethyl or methoxyisopropyl groups; an alkysilyl ester (e.g., a trimethylsilyl or triethylsilyl ester); and a tetrahydropyranyl ester.

A preferred group of prostaglandins includes 13,14-dihydro-15-keto-PGs, which, as used herein, refer to prostaglandins in which the carbon atoms at the 13,14-positions are saturated and the carbon atoms at the 15 position forms a carbonyl group. These are found in human and animal metabolites. Examples of the preferred 13,14-dihydro-15-keto-PGs include, without limitation thereto, 13,14-dihydro-15-keto-PGA_{1s}; 13,14-dihydro-15-keto-PGA_{2s}; 13,14-dihydro-15-keto-PGA_{3s}; 13,14-dihydro-15-keto-PGB_{1s}; 13,14-dihydro-15-keto-PGB_{2s}; 13,14-dihydro-15-keto-PGB_{3s}; 13,14-dihydro-15-keto-PGC_{1s}; 13,14-dihydro-15-keto-PGC_{2s}; 13,14-dihydro-15-keto-PGC_{3s}; 13,14-dihydro-15-keto-PGA_{1s}; 13,14-dihydro-15-keto-PGA_{2s}; 13,14-dihydro-15-keto-PGA_{3s}; 13,14-dihydro-15-keto-PGD_{1s}; 13,14-dihydro-15-keto-PGD_{2s}; 13,14-dihydro-15-keto-PGD_{3s}; 13,14-dihydro-15-keto-PGE_{1s}; 13,14-dihydro-15-keto-PGE_{2s}; 13,14-dihydro-15-keto-PGE_{3s}; 13,14-dihydro-15-keto-PGF_{1s}; 13,14-dihydro-15-keto-PGF_{2s}; 13,14-dihydro-15-keto-PGF_{3s}; 13,14-dihydro-15-keto-PGJ_{1s}; 13,14-dihydro-15-keto-PGJ_{2s}; and 13,14-dihydro-15-keto-PGJ_{3s}.

More preferred are 13,14-dihydro-15-keto-20-loweralkylprostaglandins, as disclosed in U.S. Patent No. 5,208,256, which is incorporated herein by reference. A particularly preferred prostaglandin is isopropyl unoprostone or 13,14-dihydro-15-keto-20-ethyl $PGF_{2\alpha}$ isopropyl ester. The structure of isopropyl unoprostone is given below and a method of preparation is outlined in U.S. Patent 5,212,200, which is incorporated by reference.



The preferred prostaglandin concentration is an amount which will substantially reduce intraocular pressure (IOP) of an eye which has elevated IOP, especially in a patient suffering from glaucoma. Clearly the required concentration depends on a number of factors, including the efficacy of the prostaglandin in the presence of the other components,

the volumetric amount of medicament applied, and the frequency and duration of application.

It has been determined that concentrations of active agents within the range of about 0.001 to about 0.30 weight percent are more efficacious for reducing intraocular pressure than concentrations above or below this range. In particular, a concentration of about 0.06 to about 0.24 weight percent active agent is preferred, while a concentration of about 0.10 to about 0.20 is more preferred. However, the preferred concentration in any specific application depends on a number of factors, such as the concentrations and chemical nature of other ingredients as well as the delivery method and conditions. Moreover, quite unexpectedly, further increases in active agent concentrations outside these preferred ranges may actually cause less of the desired decrease in intraocular pressure than the concentrations in the preferred ranges.

B. SURFACTANTS

A surfactant, as used herein, refers to a surface active agent which improves the solubility of a substance, e.g. an active or drug, in a solvent. A non-ionic surfactant, as used herein, refers to a surfactant which possesses no easily ionizable groups.

U.S. Patent No. 5,208,256 discloses the use of Polysorbate 80 as a surfactant for prostaglandin-containing ophthalmic compositions. Polysorbate 80 improves the solubility of isopropyl unoprostone, so that a higher concentration of isopropyl unoprostone can be used in a solution form.

However, it has been discovered that while increasing the Polysorbate 80 concentration allows for increases in the prostaglandin concentration in solution, the preservative effectiveness decreases with increasing Polysorbate 80 concentrations. Moreover, it is desired to increase both the efficacy (e.g., by increasing the prostaglandin concentration) and preservative effectiveness of the known prostaglandin-containing ophthalmic formulations. Thus, it has been determined that use of more Polysorbate 80 has the disadvantage of decreasing preservative effectiveness, while less Polysorbate 80 has the disadvantage of reducing prostaglandin in solution and thereby reducing efficacy.

One embodiment of the present invention offers a solution to these problems by using a combination of two or more non-ionic surfactants. Certain combinations of non-ionic surfactants have been found to increase prostaglandin active agent solubility without

reducing preservative effectiveness as much as Polysorbate 80 alone in the same concentration.

A preferred group of non-ionic surfactants are those which exhibit better ophthalmic tolerance than Polysorbate 80 alone and/or which do not reduce preservative effectiveness or reduce preservative effectiveness less than Polysorbate 80 alone in the same concentration.

The first and second non-ionic surfactants may be selected from a group of non-ionic surfactants including, without limitation thereto, polyoxyethylene sorbitan fatty acid esters such as Polysorbates 20, 60 and 80; polyoxyethylene alkyl ethers such as Brij's (e.g., BRIJ 97 or BRIJ 98 from ICI Surfactants, Wilmington, Delaware), Cremophors (such as Cremophor RH or Cremophor EL), Volpo (e.g., VOLPO 10 and VOLPO 20 from Croda, Inc., Parsippany, New Jersey) and equivalents thereof. A preferred group includes polyoxyethylene 20 oleate (e.g., Polysorbate 80), Polyoxyl 10 oleyl ethers (e.g., Brij 97) and Polyoxyl 20 oleyl ethers (e.g., Brij 98).

A particularly preferred combination of surfactants is the combinations of a polyoxyethylene sorbitan fatty acid ester (especially Polysorbate 80) with a polyoxyethylene alkyl ethers (especially BRIJ 97 or BRIJ 98).

Thus, use of at least two surfactants together provides an unexpected synergistic result in that the total concentration of surfactant required to achieve a desired prostaglandin active agent solubility is less that the concentration required for an individual surfactant. In addition, certain combinations of surfactants actually improve the preservative effectiveness. Specifically, the combination of Polysorbate 80 with a BRIJ surfactant improves BAK preservative effectiveness relative to the same concentration of Polysorbate 80 alone. Furthermore, this combination of surfactants improves the emulsion stability of the formulation.

The total concentration of surfactant used depends, in large part, on the solubilizing character of the particular surfactant or surfactants and the concentration and chemical nature of the particular prostaglandin active agent which the surfactant is intended to solubilize. In general, the total surfactant concentration may range from about 0.1 to 5 weight percent. A preferred surfactant concentration is about 0.3 to 2.0 weight percent. More preferably, the surfactant concentration is about 0.5 to 1.5 weight percent.

C. PRESERVATIVES AND PRESERVATIVE ENHANCERS

A "preservative", as used herein, refers to an additive which inhibits both microbial growth and kills microorganisms which inadvertently contaminate the ophthalmic solution upon exposure to the surroundings. The preservative may be selected from a variety of well known preservatives, including hydrophobic or non-charged preservatives, anionic preservatives, and cationic preservatives. A "preservative enhancing agent", as used herein, refers to an additive which increases the preservative effectiveness of a preservative, or the preservative effectiveness of a preserved formulation, but which would not typically be used solely to preserve an ophthalmic formulation.

1. Strong Preservatives

Cationic preservatives include, without limitation thereto, polymyxin B sulfate, quaternary ammonium compounds, poly(quaternary ammonium) compounds, p-hydroxybenzoic acid esters, certain phenols and substituted alcohols, benzalkonium chloride, benzoxonium chloride, cetylpridinium chloride, benzethonium chloride, cetyltrimethyl ammonium bromide, chlorhexidine, poly(hexamethylene biguanide), and mixtures thereof. Poly(quaternary ammonium) compounds include BUSAN 77, ONAMER M, MIRAPOL A15, IONENES A, POLYQUATERNIUM 11, POLYQUATERNIUM 7, BRADOSOL, AND POLYQUAT D-17-1742. A preferred preservative for the ophthalmic field is benzalkonium chloride.

Anionic preservatives include, without limitation thereto, 1-octane sulfonic acid (monosodium salt); 9-octadecenoic acid (sulfonated); ciprofloxacin; dodecyl diphenyloxide-disulfonic acid; ammonium, potassium, or sodium salts of dodecyl benzene sulfonic acid; sodium salts of fatty acids or tall oil; naphthalene sulfonic acid; sodium salts of sulfonated oleic acid; organic mercurials such as thimerosal (sodium ethylmercurithiosalicylate); thimerfonate sodium (sodium p-ethylmercurithiophenylsulfonate).

Hydrophobic or non-ionic preservatives include, without limitation thereto, 2,3-dichloro-1,4-naphthoquinone; 3-methyl-4-chlorophenol (PREVENTOL CMK); 8-hydroxyquinoline and derivatives thereof; benzyl alcohol; bis(hydroxyphenyl) alkanes; bisphenols; chlorobutanol; chloroxylenol; dichlorophen [2,2'-methylene-bis(4-chlorophenol)] (PANACIDE); ortho-alkyl derivatives of para-bromophenol and para-chlorophenol; oxyquinoline; para-alkyl derivatives of ortho-chlorophenol and ortho-bromophenol; pentachlorophenyl laurate (MYSTOX LPL); phenolic derivatives such as 2-phenylphenol, 2-benzyl-4-chlorophenol, 2-cyclopentyl-4-

chlorophenol, 4-t-amylphenol, 4-t-butylphenol, and 4- and 6-chloro-2-pentylphenol; phenoxy fatty acid polyester (PREVENTOL B2); phenoxyethanol; and phenylethyl alcohol.

In one embodiment, the preservative is present in the solution in an amount sufficient to kill microbes which may inadvertently enter the dispensing container over the period of use. The desirable concentration will depend on a number of factors, including the strength of the preservative, the conditions of dispenser use, and the length of time the dispenser and solution will be in service. Generally, the strong preservative may be present in a concentration from about 0.00005 to about 0.2 weight percent, more preferably the concentration is about 0.005 to about 0.2 weight percent, and even more preferably, the strong preservative concentration is about 0.01 to about 0.015 weight percent.

2. Preservative Enhancers

An ophthalmically acceptable agent which enhances the effectiveness of the preservative may be advantageously added to the formulation. Examples of preservative enhancing agents useful in accordance with the present invention include, without limitation thereto, chelating agents such as ethylene diamine tetraacetate (EDTA), derivatives thereof, salts thereof and mixtures thereof.

The preservative enhancing agent is intended to overcome any remaining microbial burden which the strong preservative did not. For example, while BAK kills nearly all *Pseudomonas*, there may remain some resistant strain or strains, which may propagate over time. Thus, it is desirable to add a preservative enhancing agent, such as EDTA, to kill the remaining BAK-resistant *Pseudomonas*. It is believed that EDTA destroys the *Pseudomonas* by chelation with Ca^{+} ions. Accordingly, a preferred class of weak preservatives are chelating agents, especially calcium chelating agents.

The use of EDTA is particularly preferred in part because EDTA prevents the growth of BAK-resistant *Pseudomonas*. However, EDTA has also been found to have advantages in addition to its preservative enhancing function. EDTA can be used to buffer the formulation to achieve the desired pH. Further, EDTA may provide a stabilization function for the prostaglandin active agent, thereby inhibiting degradation and increasing shelf life.

The concentration of preservative enhancing agent which is preferred will depend on a number of factors, such as the efficacy of the strong preservative at the chosen concentration and the preservative enhancing effectiveness of the preservative enhancing

agent. The concentration of preservative enhancer should be high enough to deactivate amounts of *Pseudomonas* which are dangerous to the patient, but the concentration should be low enough to avoid any substantial ocular discomfort.

If a chelating agent such as EDTA is used, a concentration of about 0.01 to about 0.1 weight percent is preferred. More preferably, the concentration is about 0.03% to about 0.07%.

Another additive which was determined, quite unexpectedly, to enhance the preservative effectiveness of formulations containing prostaglandin active agents is mannitol. It is known to use mannitol to adjust tonicity of an solution to improve ophthalmic compatibility, e.g., by adjusting to nearly an isotonic state. However, the preservative enhancing effect was unexpectedly found in formulations containing prostaglandin active agents. In general, it is believed that other non-ionic tonicity adjusting agents, especially other simple sugars, may perform the same function.

Thus, use of one or more preservative enhancers can provide at least two advantages. First, the amount of strong preservative, which may cause irritation to some patients, required for a given level of preservation is reduced. Second, the preservative enhancers may be chosen so that they serve functions in addition to improving preservation of the formulation.

3. Weak Preservatives

An additional weaker preservative may be added to the container. The weaker preservative, at the concentrations of use, should not be sufficiently potent to cause irritation of the target tissue which the solution will contact. Examples of weaker preservatives useful in accordance with the present invention include, without limitation thereto, peroxides, such as hydrogen peroxide; peroxide-generating species, such as an alkali perborate or a combination of sodium perborate, boric acid, and sodium borate; urea peroxide; sodium peroxide carbonate; sodium persulfate; sodium perphosphate; and poly(vinyl pyrrolidone) hydrogen peroxide. A preferred weak preservative is a perborate such as sodium perborate.

If a peroxide or peroxide-generating species is used, the peroxide concentration should be less than about 0.1 weight percent, preferably about 0.004 to 0.05 weight percent, more preferably about 0.001 to 0.02 weight percent.

D. BUFFERS AND pH

The addition of a buffer offers at least two advantages. First, the buffer helps maintain the pH of the formulation at an ophthalmically acceptable level for instillation directly into the eye. Second, incorporating a buffer early in the manufacturing process reduces the complexity of controlling the pH during manufacturing.

A variety of ophthalmically acceptable buffers may be used. For example, borate buffers such as a combination of boric acid and sodium borate, phosphate buffers, citrates, lactates, equivalents thereof and mixtures thereof.

Also, as mentioned earlier EDTA, which is a preferred weak preservative, may serve a buffering function. Thus, EDTA may advantageously be used to serve at least two functions, i.e., to adjust and maintain the pH and to act as a preservative enhancer. It should be noted that EDTA may further serve as a stabilizer for the active agent, i.e., inhibiting degradation of the active agent (e.g., by chelating metal ions which may catalyze degradation or acting as an antioxidant).

E. TONICITY ADJUSTING AGENTS

Tonicity adjusting agents may be added to the ophthalmic compositions in order to improve ophthalmic compatibility, i.e., to adjust tonicity to approximate that of the tears. A wide variety of tonicity adjusting agents may be used. Useful ophthalmic tonicity adjusting agents include, without limitation thereto, sodium chloride, mannitol, benzalkonium chloride, phedrine chloride, procaine chloride, chloramphenicol, sodium citrate, mixtures thereof or the like.

However, non-ionic tonicity adjusting agents are preferred in order to maximize the solubility of the non-ionic prostaglandin. Examples of useful non-ionic tonicity adjusting agents include mannitol, sorbitol, glycerol, polyethylene glycols (PEG), polypropylene glycols (PPG), sorbitol and mixtures thereof.. A preferred non-ionic tonicity adjusting agent is mannitol.

In addition to the unexpected enhancement of preservative effectiveness, certain non-ionic tonicity adjusting agents may serves additional functions in ophthalmic formulations containing prostaglandin active agents. For example, it has been unexpectedly discovered that mannitol increases the solubility of isopropyl unoprostone, a preferred active agent.

Thus, use of appropriate non-ionic tonicity adjusting agents can (1) result in lower requirements for strong preservatives, which may cause ocular irritation, (2) reduce the concentration of solubility enhancers and/or reduce the amount of active agent required to achieve a chosen active concentration in solution, and (3) adjust the tonicity to ophthalmically acceptable levels.

The tonicity adjusting agent concentration is typically determined by adding sufficient tonicity adjusting agent to produce a formulation with is substantially isotonic, in order to maximize patient comfort. An isotonic solution is one which may be expressed as having a concentration equivalent to about 0.9 mg/ml sodium chloride in deionized water. Substantially isotonic, as used herein, refers to a formulation having about 0.8 to 1.0 mg/ml NaCl equivalents.

In order to achieve a substantially isotonic solution, about 0.1 to 10 weight percent of non-ionic tonicity adjusting agent should be added to the formulation. More preferably, the formulation will include about 1 to 7 weight percent of non-ionic tonicity adjusting agent. Even more preferably, the formulation will include about 3 to 5 weight percent of non-ionic tonicity adjusting agent.

F. OPHTHALMICALLY ACCEPTABLE CARRIERS

A preferred solvent for the present invention is water, for example, in the form of distilled water or physiological saline. However, the invention is not limited to a particular solvent or diluent, except that the solvent must be ophthalmically compatible under the conditions of intended use. Other examples of diluents for producing a non-aqueous suspension include, without limitation thereto, edible oils, liquid paraffins, mineral oil, propylene glycol, p-octyldodecanol, mixtures thereof and the like.

G. OTHER OPHTHALMICALLY ACTIVE AGENTS

While the prostaglandin formulations described herein are useful in treating ocular hypertension without additional actives, additional actives may be desirable and are within the scope of the invention. For example, the present formulations may include conventional cholinergic ocular hypertensive agents such as pilocarpin or carbachol; anticholinesterases such as demecarium, D.F.P. or echothiophate; miotics such as physostigmine salicylate or pilocarpine hydrochloride; and antiinflammatories such as diclofenac, penicillin, sulfonamide, chloramphenicol, cortisone or chlorpheniramine.

The aforementioned actives are listed to further the reader's understanding of the various embodiments of the invention. Thus, the list of actives, provided above for addition to the present formulations, is not exhaustive and the invention is not so limited.

III. METHODS OF USING THE COMPOSITIONS

The present ophthalmic compositions may be applied to the ocular tissue or ocular fluids via a number of techniques. For example, a solution or slurry of the ophthalmic composition may be directly instilled into the eye in a droplet, spray or mist form. Alternatively, a drug delivery device with a reservoir (e.g., a polymeric network), which holds the ophthalmic composition, may be inserted into the ocular cavity (e.g., under the eyelid) and left for an extended period of time. The compositions may also be applied transdermally, including by electrotransport, preferably to skin areas near the eye. Injection, either subcutaneous or intraocular, and oral administration may also be useful delivery routes.

However, application of the ophthalmic compositions to the ocular fluids by dropwise addition is currently a preferred method. The number of drops and number of applications per day may vary, depending, *inter alia*, on the composition efficacy, patient tolerance and relative state of the disease.

Thus, one embodiment of the invention is a method of reducing ocular hypertension, which involves administering to the ocular fluids or ocular tissue an ophthalmic composition including a prostaglandin active agent which is selected from the group consisting of prostaglandins, metabolites thereof, derivatives thereof, salts thereof, and mixtures thereof; an ophthalmic preservative; a non-ionic tonicity adjusting agent; and an ophthalmically acceptable carrier. The non-ionic tonicity adjusting agent is preferably present in a concentration sufficient both to adjust the tonicity of the composition and to increase the preservative effectiveness. The composition is effective in lowering intraocular pressure when administered to a patient in need of a reduction in intraocular pressure.

Another embodiment of the invention is a method of reducing ocular hypertension, which includes administering to the ocular fluids or ocular tissue an ophthalmic composition including a prostaglandin active agent; a first non-ionic surfactant; a second non-ionic surfactant; and an ophthalmically acceptable carrier. The total surfactant concentration is lower than the surfactant concentration which would be required to solubilize the prostaglandin active agent for either individual non-ionic surfactant.

Yet another embodiment is a method of reducing ocular hypertension, which includes administering to the ocular fluids or ocular tissue an ophthalmic composition including a prostaglandin active agent; a strong preservative; a non-ionic surfactant which increases solubility of the prostaglandin active agent but decreases the preservative effectiveness of the strong preservative; a preservative enhancer which increases the effectiveness of the strong preservative; and an ophthalmically acceptable carrier.

The previous disclosure will enable one having ordinary skill in the art to practice the invention. In order to better enable the reader to understand specific embodiments and the advantages thereof, reference to the following examples is suggested. However, the invention is not limited to the various embodiments illustrated in the Examples; the Examples are merely provided to enhance the reader's understanding of the invention.

EXAMPLE 1

A 0.12% isopropyl unoprostone ophthalmic formulation was prepared in accordance with the following procedure. A surfactant solution was prepared by dissolving about 0.517 grams of Polysorbate-80 and about 0.221 grams of Brij-97 were dissolved in about 70 grams of distilled water. The surfactant solution was added to about 0.132 grams of isopropyl unoprostone (Ueno Fine Chemicals, Osaka, Japan) and stirred overnight. About 1.034 grams of about 1.06 weight percent benzalkonium chloride (BAK) solution, about 11.0 grams of 0.01 molar phosphate buffer, and about 0.011 grams of ethylenediamine tetraacetate (EDTA) were added to the isopropyl unoprostone solution and mixed until dissolved. Distilled water was added to the resultant solution to bring the weight up to 90% of the final desired weight (110 grams). About 5.153 grams of mannitol was added to the solution, with stirring until dissolved. Finally, distilled water was added to bring the solution to a final weight of 110 grams.

The resultant solution had a composition, based on weight, of:

0.12% isopropyl unoprostone,
0.47% Polysorbate 80,
0.20% Brij 97,
0.011% BAK,
0.01% EDTA, and
4.7% mannitol.

A clear solution was observed. Accordingly, the surfactants, which had a total weight percentage of 0.67%, completely solubilized the isopropyl unoprostone.

About 30 microliters of the formulation were instilled into the eye of a rabbit at time designated as t=0. The intraocular pressure (IOP) was measured at t=0, 30, 60, 120, 180, 240, 300, and 360 minutes after instillation. IOP was measured by pneumatonometry. IOP, expressed as an average of the samples studied and as a percentage of the t=0 pressure, is shown in TABLE I.

EXAMPLE 2

An isopropyl unoprostone ophthalmic formulation was prepared substantially in accordance with the procedure of Example 1, with the exceptions being that formulation included, in weight percentages: 0.18% isopropyl unoprostone, 0.70% Polysorbate 80 and 0.30% Brij 97. Furthermore, no phosphate buffer was necessary, but pH was adjusted with NaOH. The isopropyl unoprostone was completely solubilized as in Example 1.

The IOP lowering effect of this formulation was tested substantially in accordance with the procedure described in Example 1. Intraocular pressure, expressed as a percentage of the t=0 pressure, is shown in TABLE I.

EXAMPLE 3

An isopropyl unoprostone ophthalmic formulation was prepared substantially in accordance with the procedure of Example 1, with the exceptions being that formulation included, in weight percentages: 0.24% isopropyl unoprostone, 0.95% Polysorbate 80 and 0.42% Brij 97. The isopropyl unoprostone was completely solubilized as in Example 1.

The IOP lowering effect of this formulation was tested substantially in accordance with the procedure described in Example 1. Intraocular pressure, expressed as a percentage of the t=0 pressure, is shown in TABLE I.

Examination of the data generated from the Examples 1-3 shows that a 0.18% isopropyl unoprostone is more effective than 0.12% or a 0.24% isopropyl unoprostone formulations. Accordingly, a preferred range of isopropyl unoprostone concentrations is about 0.12% to about 0.24%. An even more preferred concentration range of isopropyl unoprostone is around 0.18%.

TABLE I

IOP as a percentage of the initial IOP

Time after instillation	**Example 1** 0.12% isopropyl unoprostone	**Example 2** 0.18% isopropyl unoprostone	**Example 3** 0.24% isopropyl unoprostone
0	100	100	100
30	105	110	111
60	99	99	110
120	88	67	82
180	93	56	80
240	108	67	84
300	109	79	83
360	110	86	92

EXAMPLE 4

An isopropyl unoprostone ophthalmic formulation was prepared substantially in accordance with the procedure of Example 1, with modifications of the relative concentration of the components. The resultant formulation in weight percentages was:

0.12% isopropyl unoprostone,
0.47% Polysorbate 80,
0.20% Brij 97,
0.010% BAK,
0.01% EDTA, and
4.4% mannitol.

Thus, the total surfactant concentration was 0.67%. The isopropyl unoprostone was completely solubilized as in Example 1. Comparative results are presented in Table II.

EXAMPLE 5

An isopropyl unoprostone ophthalmic formulation was prepared substantially in accordance with the procedure of Example 2, with modifications of the relative concentration of the components, including a substitution of Volpo 10 for Brij 97. The resultant formulation in weight percentages was:

0.12% isopropyl unoprostone,
0.47% Polysorbate 80,
0.20% Volpo 10,

0.013% BAK,
0.05% EDTA, and
4.3% mannitol.

Thus, the total surfactant concentration was 0.67%. The isopropyl unoprostone was completely solubilized as in Example 1. Comparative results are presented in Table II.

EXAMPLE 6

A 0.12% isopropyl unoprostone ophthalmic formulation was prepared in accordance with the following procedure. About 6 grams of sodium chloride and about 0.2 grams of benzalkonium chloride were dissolved in about a liter of distilled water. About 0.12 grams of isopropyl unoprostone and about one (1) gram of Polysorbate 80 were mixed into the BAK solution. The resultant formulation in weight percentages included:

0.12% isopropyl unoprostone,
1.0% Polysorbate 80,
0.020% BAK,
0.6% sodium chloride

Thus, the total surfactant concentration was 1.0%. The isopropyl unoprostone was solubilized, i.e., the solution appeared clear. Comparative results are presented in Table II.

EXAMPLE 7

A 0.12% isopropyl unoprostone ophthalmic formulation was prepared substantially in accordance with Example 6, with the exception being that a reduced amount of Polysorbate 80 was used. The resultant formulation included:

0.12% isopropyl unoprostone,
0.85% Polysorbate 80,
0.020% BAK,
0.6% sodium chloride

Thus, the total surfactant concentration was 0.85%. The isopropyl unoprostone was solubilized, i.e., the solution appeared clear. Comparative results are presented in Table II.

EXAMPLE 8

A 0.12% isopropyl unoprostone ophthalmic formulation was prepared substantially in accordance with Example 7, with the exception being that a reduced amount of Polysorbate 80 was used. The resultant formulation included:

0.12% isopropyl unoprostone,
0.80% Polysorbate 80,
0.020% BAK,
0.6% sodium chloride

Thus, the total surfactant concentration was 0.80%. The isopropyl unoprostone was not completely solubilized, i.e., the solution appeared cloudy. Comparative results are presented in Table II.

The isopropyl unoprostone was not completely solubilized, i.e., phase separation was observed. Comparative results are presented in Table II.

TABLE II

	Example 1	Example 4	Example 5	Example 6	Example 7	Example 8
% isopropyl unoprostone	0.12	0.12	0.12	0.12	0.12	0.12
% Polysorbate 80	0.47	0.47	0.47	1.0	0.85	0.80
% Brij 97	0.20	0.20	--	--	--	--
% Volpo 10	--	--	0.20	--	--	--
Total % surfactant	0.67	0.67	0.67	1.0	0.85	0.80
Solubility	complete	complete	complete	complete	complete	incomplete cloudy formulation

Examples 1 and 4-8, along with Table II, show that the combination of Polysorbate 80 with Brij 97 or Volpo 10 solubilizes isopropyl unoprostone better than Polysorbate 80 alone. In Example 8, a 0.80% total surfactant formulation with Polysorbate 80 alone did not adequately solubilize the active, while a 0.67% total surfactant formulation with the combination of surfactants provided complete solubility. Thus, a lower total surfactant

concentration may be achieved by using two or more surfactants rather than one surfactant in a formuation containing prostaglandin active agents.

EXAMPLE 9

About a 100 gram ophthlamic formulation including 0.12% isopropyl unoprostone was prepared in accordance with the following procedure. About 0.12 grams isopropyl unoprostone and about 1.0 grams Polysorbate 80 were added to a beaker, followed by about 90 grams distilled water. The mixture was stirred until dissolved. About 1.2 grams of an about 1% BAK solution and about 0.05 grams EDTA were added to the resultant solution. About 3.3 grams of mannitol was added with mixing until dissolution was achieved.

The resultant formulation contained:

0.12% isopropyl unoprostone
1.0% Polysorbate 80
0.012% BAK
0.05% EDTA
3.3% mannitol

The formulation was subject to standard U.S. Pharmacopia and European Pharmacopia Criteria "A" and "B" preservative effectiveness testing. The formulation passed all three tests. Results are summarized in Table III.

EXAMPLE 10

A formulation was prepared substantially in accordance with the procedure described in Example 9, except that sodium chloride was used as the tonicity adjusting agent instead of mannitol. The formulation had the following composition:

0.12% isopropyl unoprostone
1.0% Polysorbate 80
0.012% BAK
0.05% EDTA
0.6% sodium chloride

The formulation failed the European Pharmacopia Criteria "A" and "B" preservative effectiveness tests, while passing the USP test. Results are summarized in Table III.

EXAMPLE 11

A formulation was prepared substantially in accordance with the procedure described in Example 9, except that sodium chloride was used as the tonicity adjusting agent instead of mannitol and additional BAK and EDTA were used. The formulation had the following composition:

0.12% isopropyl unoprostone
1.0% Polysorbate 80
0.013% BAK
0.10% EDTA
0.6% sodium chloride

The formulation failed the European Pharmacopia Criteria "A" and "B" preservative effectiveness tests, while passing the USP test. Results are summarized in Table III.

EXAMPLE 12

A formulation was prepared substantially in accordance with the procedure described in Example 9, except that additional BAK and EDTA were used as compared with Example 9. The formulation had the following composition:

0.12% isopropyl unoprostone
1.0% Polysorbate 80
0.013% BAK
0.10% EDTA
3.3% mannitol

The formulation passed the European Pharmacopia Criteria "A" and "B" tests as well as the USP test. Results are summarized in Table III.

EXAMPLE 13

A formulation was prepared substantially in accordance with the procedure described in Example 12, except that sodium chloride was substituted for mannitol and additional BAK was used as compared with Example 12. The formulation had the following composition:

0.12% isopropyl unoprostone
1.0% Polysorbate 80
0.014% BAK
0.10% EDTA
0.6% sodium chloride

The formulation failed the European Pharmacopia Criteria "A" and "B" preservative effectiveness tests, while passing the USP test. Results are summarized in Table III.

EXAMPLE 14

A formulation was prepared substantially in accordance with the procedure described in Example 13, except that additional BAK was used as compared with Example 13. The formulation had the following composition:

0.12% isopropyl unoprostone
1.0% Polysorbate 80
0.015% BAK
0.10% EDTA
0.6% sodium chloride

The formulation failed the European Pharmacopia Criteria "A" (EPA) and "B" (EPB) preservative effectiveness tests, while passing the US-Pharmacopia (USP) test. Results are summarized in Table III.

TABLE III

	Example 9	Example 10	Example 11	Example 12	Example 13	Example 14
% isopropyl unoprostone	0.12	0.12	0.12	0.12	0.12	0.12
% Polysorbate 80	1.0	1.0	1.0	1.0	1.0	1.0
% BAK	0.012	0.012	0.013	0.013	0.014	0.015
% EDTA	0.05	0.05	0.10	0.10	0.10	0.10
% mannitol	3.3	--	--	3.3	--	--
% sodium chloride	--	0.6	0.6	--	0.6	0.6
EPA	PASS	fail	fail	PASS	fail	fail
EPB	PASS	fail	fail	PASS	fail	fail
USP	PASS	PASS	PASS	PASS	PASS	PASS

Examples 9-14 and Table III illustrate that the non-ionic tonicity adjusting agent mannitol enhances preservative effectiveness as compared to the ionic tonicity adjusting agent sodium chloride.

The invention has been described in detail, with reference to certain preferred embodiments, in order to enable the reader to practice the invention without undue experimentation. However, a person having ordinary skill in the art will readily recognize that many of the components and parameters may be varied or modified to a certain extent without departing from the scope and spirit of the invention. Furthermore, titles, headings, definitions or the like are provided to enhance the reader's comprehension of this document, and should not be read as limiting the scope of the present invention. Accordingly, the intellectual property rights to this invention are defined only by the following claims and reasonable extensions and equivalents thereof.

CLAIMS

1. A composition, comprising:

(a) a prostaglandin active agent which is selected from the group consisting of prostaglandins, metabolites thereof, derivatives thereof, salts thereof, and mixtures thereof;

(b) an ophthalmic preservative;

(c) a non-ionic tonicity adjusting agent, wherein said non-ionic tonicity adjusting agent is present in a concentration sufficient to:

(i) adjust the tonicity of the composition and

(ii) increase the preservative effectiveness; and

(d) an ophthalmically acceptable carrier.

2. A composition of claim 1, further comprising a chelating agent.

3. A composition of claim 2, wherein said chelating agent is ethylenediamine tetraacetic acid or a salt thereof.

4. A composition of claim 2, comprising 0.1 to 10 weight percent non-ionic tonicity adjusting agent and 0.01 to 0.10 weight percent chelating agent.

5. A composition of claim 1, wherein said active agent is a 13,14-dihydro-15-keto-20-ethyl-$PGF_{2\alpha}$ isopropyl ester.

6. A composition of claim 1, comprising 0.001 to 0.30 weight percent of the active agent.

7. A composition of claim 6, comprising 0.06 to 0.24 weight percent of the active agent.

8. A composition of claim 7, comprising 0.10 to 0.20 weight percent of the active agent.

9. A composition of claim 1, further comprising a non-ionic surfactant.

10. A composition of claim 9, comprising about 0.1 to 5.0 weight percent of a non-ionic surfactant selected from the group consisting of polyoxyethylene sorbitan fatty acid esters, polyoxyethylene alkyl ethers, and mixtures thereof.

11. A composition of claim 9, wherein the non-ionic surfactant is Polysorbate 80 and is present at a concentration of about 0.3 to 2.0 weight percent.

12. A composition of claim 1, comprising about 0.001 to about 0.05 weight percent of an ophthalmic preservative selected from the group consisting of polymyxin B sulfate; quaternary ammonium compounds; poly(quaternary ammonium) compounds; p-hydroxy-benzoic acid esters; certain phenols and substituted alcohols; benzalkonium chloride; benzoxonium chloride; cetylpridinium chloride; benzethonium chloride; cetyltrimethyl ammonium bromide; chlorhexidine, poly(hexamethylene biguanide); 1-octane sulfonic acid (monosodium salt); 9-octadecenoic acid (sulfonated); ciprofloxacin; dodecyl diphenyloxide-disulfonic acid; ammonium, potassium, or sodium salts of dodecyl benzene sulfonic acid; sodium salts of fatty acids or tall oil; naphthalene sulfonic acid; sodium salts of sulfonated oleic acid; organic mercurials such as thimerosal; thimerfonate sodium; 2,3-dichloro-1,4-naphthoquinone; 3-methyl-4-chlorophenol; 8-hydroxyquinoline; benzyl alcohol; bis(hydroxy-phenyl) alkanes; bisphenols; chlorobutanol; chloroxylenol; dichlorophen [2,2'-methylene-bis(4-chlorophenol)]; ortho-alkyl derivatives of para-bromophenol and para-chlorophenol; oxyquinoline; para-alkyl derivatives of ortho-chlorophenol and ortho-bromophenol; penta-chlorophenyl laurate; phenolic derivatives such as 2-phenylphenol, 2-benzyl-4-chloro-phenol, 2-cyclopentyl-4-chlorophenol, 4-t-amylphenol, 4-t-butylphenol, and 4- and 6-chloro-2-pentylphenol; phenoxy fatty acid polyester; phenoxyethanol; phenylethyl alcohol; derivatives and mixtures thereof.

13. A composition of claim 1, further comprising a weak preservative selected from the group consisting of peroxides, peroxide-generating species and mixtures thereof.

14. A composition of claim 1, further comprising an ophthalmically acceptable buffer selected from the group consisting of EDTA, borates and phosphates, wherein said buffer is present in an amount sufficient to maintain the composition at a pH of 5.5 to 8.5 over a period of up to one year in storage.

15. A composition of claim 1, comprising about 0.1 to 10 weight percent of an ophthalmically acceptable non-ionic tonicity adjusting agent selected from the group consisting of mannitol, sorbitol, glycerol, polyethylene glycols (PEG), polypropylene glycols (PPG), sorbitol and mixtures thereof.

16. A composition of claim 9, comprising:

(a) about 0.001 to 0.30 weight percent of a 13,14-dihydro-15-keto-20-ethyl$PGF_{2\alpha}$ isopropyl ester effective as an ocular hypotensive agent;

(b) about 0.1 to 5.0 weight percent of a non-ionic surfactant selected from the group consisting of polyoxyethylene sorbitan fatty acid esters, polyoxyethylene alkyl ethers, and mixtures thereof;

(c) about 0.005 to about 0.2 weight percent of an ophthalmic preservative; and

(d) an ophthalmically acceptable carrier.

17. A composition of claim 1, comprising:

(a) about 0.06 to about 0.24 weight percent of a 13,14-dihydro-15-keto-20-ethyl$PGF_{2\alpha}$ isopropyl ester effective as an ocular hypotensive agent;

(b) about 0.1 to about 5.0 weight percent of a non-ionic surfactant selected from the group consisting of polyoxyethylene sorbitan fatty acid esters, polyoxyethylene alkyl ethers, and mixtures thereof;

(c) about 0.01 to about 0.015 weight percent of benzalkonium chloride;

(d) about 0.01 to about 0.10 weight percent of EDTA or a salt thereof;

(e) about 3 to 5 weight percent of an ophthalmically acceptable non-ionic tonicity adjusting agent selected from the group consisting of mannitol, sorbitol, glycerol, polyethylene glycols (PEG), polypropylene glycols (PPG), sorbitol and mixtures thereof;

(f) an ophthalmically acceptable carrier,

wherein said composition has a pH of about 4.5 to about 8.0.

18. A composition comprising:

(1) a prostaglandin active agent;

(2) a first non-ionic surfactant; and

(3) a second non-ionic surfactant; and

(4) an ophthalmically acceptable carrier,

wherein the total surfactant concentration is lower than the surfactant concentration which would be required to solubilize the prostaglandin active agent for either individual non-ionic surfactant.

19. A composition of claim 18, wherein said non-ionic surfactants are selected from the group consisting of polyoxyethylene sorbitan fatty acid esters, polyoxyethylene alkyl ethers, and mixtures thereof.

20. A composition of claim 19, wherein said first non-ionic surfactant is a polyoxyethylene sorbitan fatty acid ester and said second non-ionic surfactant is a polyoxyethylene alkyl ether.

21. A composition of claim 20, wherein said first non-ionic surfactant is a Polysorbate compound and said second non-ionic surfactant is Brij compound.

22. A composition of claim 21, wherein the total non-ionic surfactant concentration in the composition is about 0.3 to 2.0 weight percent.

23. A composition comprising:

(1) a prostaglandin active agent;

(2) a strong preservative;

(3) a non-ionic surfactant which increases solubility of the prostaglandin active agent but decreases the preservative effectiveness of the strong preservative;

(4) a preservative enhancer which increases the effectiveness of the strong preservative; and

(5) an ophthalmically acceptable carrier.

24. A composition of claim 23, wherein said preservative enhancer is selected from the group consisting of mannitol, ethylenediamine tetraacetic acid, salts thereof, and mixtures thereof.

25. A composition of claim 24, wherein said preservative enhancer is mannitol.

26. A composition of claim 24, wherein said preservative enhancer is ethylenediamine tetraacetic acid.

27. A composition of claim 24, wherein said preservative enhancer is a mixture of ethylenediamine tetraacetic acid and mannitol.

28. A method of reducing ocular hypertension, which comprises administering to the ocular fluids or ocular tissue an ophthalmic composition comprising:

(a) a prostaglandin active agent which is selected from the group consisting of prostaglandins, metabolites thereof, derivatives thereof, salts thereof, and mixtures thereof;

(b) an ophthalmic preservative; and

(c) a non-ionic tonicity adjusting agent, wherein said non-ionic tonicity adjusting agent is present in a concentration sufficient to:

(i) adjust the tonicity of the composition and

(ii) increase the preservative effectiveness; and

(d) an ophthalmically acceptable carrier,

wherein said composition is effective in lowering intraocular pressure when administered to a patient in need of a reduction in intraocular pressure.

29. A method of reducing ocular hypertension, which comprises administering to the ocular fluids or ocular tissue an ophthalmic composition comprising:

(1) a prostaglandin active agent;

(2) a first non-ionic surfactant; and

(3) a second non-ionic surfactant; and

(4) an ophthalmically acceptable carrier,

wherein the total surfactant concentration is lower than the surfactant concentration which would be required to solubilize the prostaglandin active agent for either individual non-ionic surfactant

30. A method of reducing ocular hypertension, which comprises administering to the ocular fluids or ocular tissue an ophthalmic composition comprising:

(1) a prostaglandin active agent;

(2) a strong preservative;

(3) a non-ionic surfactant which increases solubility of the prostaglandin active agent but decreases the preservative effectiveness of the strong preservative;

(4) a preservative enhancer which increases the effectiveness of the strong preservative; and

(5) an ophthalmically acceptable carrier.

31. An ophthalmic composition, comprising:

(a) about 0.06 to about 0.24 weight percent of a prostaglandin active agent which is selected from the group consisting of prostaglandins, metabolites thereof, derivatives thereof, salts thereof, and mixtures thereof;

(b) an ophthalmic preservative;

(c) a non-ionic toncity adjusting agent;

(d) a non-ionic surfactant; and

(e) an ophthalmically acceptable carrier.

32. A composition in accordance to any of the preceding claims for the treatment of ocular hypertension.

33. Use of a composition in accordance to any of the preceding claims in the preparation of an ophthalmic composition in the treatment of ocular hypertension.

INTERNATIONAL SEARCH REPORT

Inte onal Application No
PCI/EP 98/01483

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K31/557 A61K9/00

According to International Patent Classification(IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 5 558 876 A (SUKETU DESAI; ET AL.) 24 September 1996 see column 1, line 63 - column 3, line 12 see column 4; examples 3E,3F ---	1-4,6-9, 12,14, 15,28, 30-33
X	WO 95 30420 A (ALCON LABORATORIES) 16 November 1995 see claim 1 see page 1, paragraph 2 see page 2, paragraph 3 see page 8; example 2 see page 9; example 3 --- -/--	1-4,6-8, 15, 23-25, 28,30-33

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

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"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of theinternational search	Date of mailing of the international search report
3 June 1998	10/06/1998

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Ventura Amat, A

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INTERNATIONAL SEARCH REPORT

Inte· ·nal Application No
PC1/EP 98/01483

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category ·	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
X	WO 92 13836 A (ALLERGAN INC.) 20 August 1992	1,2,4, 6-12,14, 15, 23-28, 30-33
Y	see page 19; claim 5 see page 11, line 17 - page 13, line 15	5,16,17
Y	EP 0 458 587 A (KABUSHIKI KAISHA UENO SEIYAKU OYO KENKYUJO) 27 November 1991 see claims 1-8 see page 7, line 36 - line 45	5,16,17

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INTERNATIONAL SEARCH REPORT

Information on patent family members

Inter ›nal Application No
PC1/EP 98/01483

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